## REMARKS

### General

Applicants thank the Examiner for extending the courtesy of an in-person interview on December 14, 2005.

### The Invention.

The present invention provides modified forms of pullulanase which maintain the ability to catalyze the hydrolysis of an alpha-1,6-glucosidic bond, compositions which comprise the modified pullulanase, methods of making the modified pullulanase and methods of using the modified pullulanase, especially for the saccharification of starch.

### Status of the Application.

Claims 5-10, 12, 14, 15, 27-40 and 52-66 are pending in the application.
Claims 5-10, 12, 14, 15, 27-40 and 52-66 are rejected.
No claims have been amended herein.

### 35 U.S.C. §103.

The Examiner has rejected claims 5–10, 12, 14, 15, 27–29, 31–40, 52–53, 55-61 and 63–66 as allegedly obvious. The Examiner has cited at least one of three references in the §103 rejections. Applicants respectfully traverse the rejection(s).

"This rejection is based on printed publications and a patent." See June 29, 2005 Office Action, page 3. Similar statements were offered in all of the previous Office Actions asserting unpatentability under 35 USC §103. See March 30, 2005 Office Action, page 3; May 4, 2004 Office Action, page 6; January 27, 2003 Office Action, page 3; and February 12, 2002 Office Action, page 5. There was no §103 rejection in the October 17, 2003 Office Action; the response dated July28, 2003, having successfully presented a persuasive argument that the claims were non-obvious. Thus, *Applicants*

*need only show why the cited publications and patent do not render the presently claimed invention obvious in light of these three documents as there has been no notice that any other evidence is being relied upon.*

Applicants have provided a summary of the art in their response dated May 17, 2005, and is supplemented below. Therefore, the information below should be read in conjuction with the previous summary.

*Deweer, et al. (US Pat. No. 6,074,854)*

There is no teaching or suggestion to look for biologically active pullulanase fragments in Deweer *et al.*.

There is nothing in Deweer *et al.* that would suggest to or motivate the skilled artisan to truncate the *Bacillus* pullulanase or to combine its teachings with McPherson *et al.* or Albertson *et al.*

*McPherson et al. (Biochemical Soc. Trans., (1988) 16(5):723-724)*

The Examiner cites McPherson *et al.* as teaching proteolytic digestion, computer-based sequence analysis, and that the long N-terminal region lacks any catalyzing site. See page 4 of the Office Action.

Applicants note that McPherson *et al.* at best teaches that there may be some length of "the N-terminal region of pullulanase that has no defined catalytic function" for the *Klebsiella* pullulanase. ***There is no suggestion that the lack of defined catalytic function found in Klebsiella would be similarly found in an unrelated and non-homologous pullulanase.*** In addition, it is silent on whether or not other truncated pullulanases, in particular *Bacillus* pullulanases, would possess similar properties, characteristics or corresponding increases in activity.

There simply is no motivation to combine McPherson *et al.* with any of the cited art.

*Albertson et al., (Biochimca et Biophysica Acta, vol. 1354 (1) (1997):35-39)*

The Examiner cites Albertson *et al.* (Cloning and sequence of a type I pullulanase from an extremely thermophilic anaerobic bacterium, *Caldicellulosiruptor*

*saccharolyticus*. Biochimca et Biophysica Acta, vol. 1354 (1) (1997):35-39) as teaching the modification of a pullulanase isolated from *C. saccharolyticus*, wherein nearly 381 nucleotides from the 5' region of the cDNA encoding a pullulanase and that the deleted amino acid sequence is not essential for either activity or thermostability. See page 4 of the Office Action.

Applicants note that the work in Albertson *et al.* is related to "the molecular cloning of the gene ... and determination of its DNA and **predicted** amino acid sequence." (Emphasis added.)

The "truncation" of Albertson *et al.* may not have been a true truncation. The functional "truncated" pullulanase may be in fact be the full-length enzyme, the result of an internal start sequence. See page 38, top of column 1 where it states:

> "A possible internal start sequence complete with a ribosomal binding site could also be detected internally within the pullulanase gene (see Fig. 2), and this feature may explain the occurrence of enzymatic activity from the incomplete recombinant plasmid pNZ1452."

Applicants note that even if the truncated enzyme of Albertson *et al.* has a truncation of 95 amino acids (see page 38, top of column 2) from its N-terminus, this is fewer than the smallest truncation currently claimed. There is no suggestion or teaching that a longer deletion in an unrelated molecule would result in a functional enzyme.

*Claims 5–10, 14, 15, 27–40, 52–61 and 63–66*

The Examiner has rejected claims 5–10, 14, 15, 27–40, 52–61 and 63–66 as allegedly obvious over the combination of Deweer, *et al.* (US Pat. No. 6,074,854) in view of McPherson *et al.* (Biochemical Soc. Trans., (1988) 16(5):723-724) or Albertson *et al.*, (Biochimca et Biophysica Acta, vol. 1354 (1) (1997):35-39). Applicants respectfully traverse the rejection.

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be **motivated** to modify the references to arrive at the

**claimed invention.** *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). In particular,

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the *claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed." *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990)

A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to modify their teachings to yield the claimed invention, (b) discloses the elements of the claimed invention, **and** (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish **any** one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicants to withdrawal of the rejection of the claims in issue.[1] Applicants urge that the Examiner has failed to establish at least one of the requirements as discussed below.

***The Deweer/McPherson combination***

Deweer *et al.* is silent on the modification of a *Bacillus* pullulanase generally and to the specific modifications currently claimed. McPherson *et al.* is similarly silent on the modification of a *Bacillus* pullulanase generally and to the specific modifications currently claimed.

*The combination fails to suggest or motivate one of skill in the art to modify the teachings to yield the claimed invention*

The Examiner asserts that "it appears that experiments involving truncation of N-terminal amino acids in pullulanase enzymes was well known in the art." See page 4 of the Office Action. Applicants note that McPherson *et al.* states "The predicted amino acid sequences of pullulanases from *Klebsiella pnuemoniae* strains W70 ...and FG9 ... are very similar and provide the basis for the design of experiments to examine

[1] *See e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

pullulanase function." Thus, the similarity in the protein sequences was critical to designing experiments to define a functional 'core' pullulanase. However, there is very little sequence similarity between the presently claimed pullulanase and the pullulanase of McPherson *et al.* Thus, **one of skill in the art would not be motivated to combine McPherson *et al.* with DeWeer due to the lack of similarity between the pullulanases.**

*The combination fails to disclose the elements of the claimed invention*

Applicants provided their arguments for this prong in their Response dated May 17, 2005.

*The combination fails provide a reasonable expectation of success*

As previously stated, a skilled artisan would not have a reasonable expectation of success if they were to combine the references. First, there is nothing in Deweer *et al.* that indicates that a truncation of 98, 100, 102, 200 or 300 amino acids would result in an enzyme capable of catalyzing the hydrolysis of an alpha-1, 6-glucosidic bond.

Although McPherson *et al.* does teach a 170 amino acid deletion in an unrelated pullulanase there is no information provided that would allow the skilled artisan to perform a sequence alignment with a *Bacillus* pullulanase to know whether or not a similarly large deletion would work. **Notably, as noted above, McPherson *et al.* relied on the similarity between known enzymes to design their experiments.** The *Klebsiella* pullulanase of McPherson *et al.* is 120 kD whereas a *Bacillus* pullulanase is smaller. A similarly large deletion in the smaller enzyme may not work. Furthermore, there is no teaching that an even larger deletion would work. Thus, there is no reasonable expectation of success given the dissimilarity of the pullulanases in Deweer *et al.* and McPherson *et al.*.

For the foregoing reasons, the combination of Deweer *et al.* and McPherson *et al.* is inappropriate and fails to render the present invention obvious. Withdrawal of the rejection is respectfully requested.

***The Deweer/Albertson combination***

Deweer *et al.* is silent on the modification of a *Bacillus* pullulanase generally and to the specific modifications currently claimed. Albertson *et al.* is similarly silent on the modification of a *Bacillus* pullulanase generally and to the specific modifications currently claimed. Moreover, **the Albertson *et al.* "truncated" pullulanase may not have in fact been truncated,** see *supra*.

*The combination fails to suggest or motivate one of skill in the art to modify the teachings to yield the claimed invention*

In addition to the arguments presented in their response dated May 17, 2005, Applicants assert that the uncertainty of whether or not there was a "truncated" protein in Albertson *et al.* would not motivate a skilled artisan to intentionally truncate a full-length protein.

*The combination fails to disclose the elements of the claimed invention*

Applicants provided their arguments for this prong in their Response dated May 17, 2005.

*The combination fails provide a reasonable expectation of success*

Reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art. See *Micro Chem.*, 103 F.3d at 1547, 41 U.S.P.Q.2D (BNA) at 1245.

Applicants once again direct the Examiner's attention to the teachings of Albertson *et al.* to the fact that the "truncation" may be due to an internal start sequence and therefore was in fact a full-length protein. A skilled artisan would not have a reasonable expectation of success that truncating a full-length, unrelated protein would yield a functional enzyme based on the work in Albertson *et al.*

*Claim 12*

The Examiner has rejected claim 12 as allegedly obvious over of Deweer, *et al.* (US Pat. No. 6,074,854). The Examiner asserts that the cited reference teaches the claimed invention. Applicants respectfully traverse.

There is no teaching or suggestion in any of the cited references to specifically add an alanine to the N-terminus. While, as the Examiner notes, that there are only twenty amino acids not one of the cited references point directly to adding an alanine.

Withdrawal of the rejection is respectfully requested.

**CONCLUSION**

In light of the above amendments, as well as the remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7615.

Respectfully submitted,

Victoria L Boyd

Victoria L. Boyd
Registration No. 43,510

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Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304
Tel: 650-846-7500, Ext. 7615
Fax: 650-845-6504